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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/318,870 | 05/26/1999 | ANDREW H. SEGAL | 3378/80489 | 2018 |

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| EXAMINER | |
|---|---|
| BELYAVSKYI, MICHAIL A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/318,870 | SEGAL, ANDREW H. | |
| | Examiner | Art Unit | |
| | Michail A Belyavskyi | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,13,14,17-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13,14,17-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/24/03 is acknowledged.

Claims 1-8, 13-14, 17-20 and 22-25 are pending.

In view of the amendment, filed 10/24/03 , the following rejections remain

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

3. Claims 1-8, 13, 14, 17-20 and 22-25 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least 20 % increasing in a survival period of vaccinated mice compare to control non-vaccinated mice during B16 cells –initiated melanoma tumor formation comprising vaccinated mice with composition comprising cytokine-coated B16 cells, does not reasonably provide enablement for a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed 04/22/03.

Applicant's arguments, filed 10/24/03 , have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the specification teaches on paged 16-47 more than six different families of cytokines useful in the invention , on pages 68-71 various antigens useful in the method of the invention, on pages 71-76 method for expressing nucleic acid molecules encoding antigens, on pages 76-77 multiple cell types which may be used according to the invention, on pages 104-107 methods for administering the vaccine of the invention, including methods for preparing pharmaceutical formulation; (ii) the term "vaccinating" defined as the modulation of an immune response to a selected antigen and that applicant is not required to provide data demonstrating the ability of the vaccine composition of the invention to protect or prevent from antigen-specific disease, since the present invention is based on the discovery that the admixture of a cell bearing a given antigen with an exogenous cytokine results in a vaccine composition which is capable of effectively targeting the antigen to an antigen presenting cell; (iii) The

Declaration under 37 C.F.R.1.132 by Dr. Andrew Segal provides data to show that the vaccine composition of the present invention are effective in vaccinating a mammal to which they are administered.

Contrary to Applicants assertion, the issue raised in the previous Office Action, was that the specification only discloses that mice vaccinated with cytokine-coated melanoma B16 cells will have a considerably longer survival period as compare to control mice ( see examples 7-9 in particular). Similarly, the Declaration under 37 C.F.R.1.132 by Dr. Andrew Segal provides only data demonstrating the ability GM-CSF-coated CMS-5 fibrosarcoma cells to increase a survival period of vaccinated mice compare to control non-vaccinated mice during CSM-5 – initiated fibrosarcoma tumor formation.

With regards to the issue that Applicant defines the term " vaccinating" as the modulation of the immune response. The examiner acknowledge that while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Moreover, during examination, claims are to be interpreted as broadly as their term reasonably allow because ambiguity and undue breadth of the language can be readily corrected to fashion a claim which is precise, clear, correct and unambiguous. *In re Zletz,* 13 USPQ2d 1320 (Fed.Cir. 1989).

It is noted that the instant claims recited a method of vaccinating a mammal to a selected antigen, not a method of modulating the immune response or a method of effectively targeting the antigen to an antigen presenting cell, as asserted by Applicant. By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent. Applicant himself acknowledge that one of aspects of the invention is protection ( between 5 to 100 %) against tumors ( see Applicant's Arguments, filed 10/24/03, pages 13 and 14 in particular). One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of antigen - specific antibody. The second criterion for a vaccine is the ability to stimulate memory T lymphocytes (cell-mediated immune response) (See Immunobiology, Third Edition, Chapter 13 in particular). The specification provides no information on the immunogenicity of *any* vaccine comprising *any* cytokine-coated cell comprising antigen or the ability of such to protect or prevent from antigen-specific disease. Moreover, Applicant acknowledge that tumors were detected in mice vaccinated with composition comprising cytokine-coated B16 cells ( see page 101, line 16-20 in particular). The specification fails to teach that the vaccine comprising *any* cytokine-coated cell comprising antigen are capable of generating an antibody response. The specification also fails to teach that the antibody response to the claimed *any* cytokine-coated cell comprising antigen thereof, provides for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds)

published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". Moreover, Chandrasheker et al., (US Patent 6,248,329) teach that although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessary correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from specific disease, associated with said antigen ( see column 1, lines 35-45 in particular). In addition, Spitler , (Cancer Biotherapy, 1995, v.10 pages 1-3 teaches that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response" ( see page 1, column 1, paragraph 1 in particular). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (NIH Research, 1995, Vol.7, pages 46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

The specification fails to teach that claimed *any* cytokine-coated cell comprising antigen does in fact confer protection from infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to teach that the claimed *any* cytokine-coated cell comprising antigen is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize *any* cytokine-coated cell comprising antigen as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. ( Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen exemplified in the specification.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates

that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> *(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.*

5. Claims 1, 2, 13, 14, 17-19, 22-25 stands rejected under 35 U.S.C. 102(e) as being anticipated by Hiserodt et al. (US Patent 6,277,368) for the same reasons set forth in the previous Office Action, mailed 04/22/03.

Applicant's arguments, filed 10/24/03 , have been fully considered, but have not been found convincing.

Applicant submits that US Patent '368 does not teach vaccine composition comprising a cytokine coated cells comprising an exogenous cytokine.

Contrary to Applicant's Assertion, it is the examiner position, that US Patent '368 teaches a method of vaccinating a mammal, including mouse , to selected antigen, comprising administering a vaccines comprising a primary tumor cells and cytokine-secreting cells ( see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cell that already express an antigen, a tumor cell antigen for example, with engineered cytokines that can become membrane-bound ( see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells ( see column 7, lines 25-40 in particular). US Patent '368 teaches that cytokine is a GM-CSF, that is a ligand for GM-CSF receptor ( see column 7, lines 31, or column 10, lines 52-65 in particular). US Patent '368 teaches that said cytokines can be membrane-bound capable of potentiating an immunological response against the tumor-associated antigen ( column 15, lines 36-45 in particular). US Patent '368 teaches a immunogenic composition comprising 2 population of cells: first population is tumor cells i.e. specific antigen expressing cells and second population is the cytokine-producing cells ( see column 15, line 35-40 and claim 9 in particular). Cytokines secreted by said second cytokine-secreting cells would be exogenous cytokines that are produced outside of first population of antigen expressing cells, that will become "cytokine-coated cells", wherein said cytokine of said

cytokine-coated cells is exogenous to said antigen expressing cell. Moreover, US Patent '368 teaches that it is preferable that cytokine attached to the cell membrane to keep it in the vicinity of bystander tumor antigen comprised in the vaccine ( see column 16, lines 28-35 in particular). US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity ( see column 16, line 50-65 in particular). US Patent '368 teaches that said vaccine composition can be attenuated ( see overlapping columns 23 and 24 in particular).

Claims 22 and 25 are included because the claimed functional limitation would be inherent properties of the referenced method , because it is clear that both the prior art and claimed invention administer the same treatment to achieve the same results using the same extremely bioactive, natively bioactive or suprabioactive cytokines and cytokine-coated cells that would be unable to divide in vitro . Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. Since the office does not have a laboratory to test the reference cytokines it is applicant's burden to show that the reference cytokines do not have the same functional limitation as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teaching anticipates the claimed invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

7. Claims 3-8 and 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Hiserodt et al. (US Patent 6,277,368) in view of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 for the same reasons set forth in the previous Office Action, mailed 04/22/03.

Applicant's arguments, filed 10/24/03 , have been fully considered, but have not been found convincing.

Applicant asserts that there is no teaching whatsoever in US Patent '368 of the use of an opsonin-enhanced cells and this is a clear instance of hindsight reconstruction of Applicant's invention.

Applicants have traversed the primary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

The teaching of US Patent '368 has been discussed, supra. US Patent '368 teaches that cytokines can be engineered to become stable associated with the plasma membrane ( see column 16, lines 50-65 in particular). US Patent '368 does not teach specific types of engineered cytokine or specific opsonin-enhanced cells as recited in claims 3-8 and 20.

The Known fact disclosed in the Specification on pages 52-54 and 66 – 68 teaches that it is conventional and within the skill of the art to produce : (i) an opsonin-enhanced cells, wherein opsonin of said cells is mannose binding protein or alph' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching the lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety to said cytokine to permit a complex to become stable associated with plasma membrane.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 to those of US Patent '368 to obtain a claimed method of vaccinating a mammal to a selected antigen, comprising administering vaccine composition comprising an opsonin-enhanced cells and engineered cytokine comprising a lipid or GPI moiety or palmitate.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because engineered cytokine wherein lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety is attached to said cytokine permits said complex to become stable associated with plasma membrane of the cell and an opsonin-enhanced of said cells, allows more efficient binding, engulfment and internalization of said engineered cytokine into said cell as taught by the known fact disclosed in the Specification on pages 52-54 and 66-68. Thus the "cytokine-coated cells " will be obtained that can be further used by the method taught by US patent '368.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Michail Belyavskyi, Ph.D.
Patent Examiner
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January 6, 2004

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